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TO:	Examiner G. Gabel United States Patent and Trademark Office	**NUMBER OF PAGES (INCLUDING THIS TRANSMITTAL SHEET):**	22
FAX:	703-308-4242	**PHONE:**	703-305-0807
DATE:	April 23, 2001		
FROM:	Mark J. Murphy		
REFERENCE:	Patent Application Serial No. 09/382,622 Our Ref. No. PHO-107 DIV		

MESSAGE:

If you experience difficulty receiving this facsimile transmission, or a portion thereof, please contact Christine Muilenburg at 312-236-8500 for immediate assistance.

Attorney Docket no: PHO-107 DIV

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

Dees et al.

Serial No.: 09/382,622

Filed: August 25, 1999

For: High Energy Phototherapeutics Agents

Examiner: G. Gabel

Art Unit: 1641

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: the Commissioner for Patents, Washington, D.C. 20231 on

Christine Muilenburg

Signature Date

April ___, 2000

Assistant Commissioner for Patents
Washington D.C. 20231

-- DRAFT --

AMENDMENT B (AFTER FINAL)

In response to the Final Rejection of February 27, 2001, please amend the above-identified application as follows:

IN THE SPECIFICATION:

Please amend page 1 of the specification as shown in the attached pages.

IN THE CLAIMS:

Please amend the claims as follows:

1 (Twice Amended). A radiosensitizer agent for treatment of cancer and tumors using applied ionizing radiation, said radiosensitizer agent comprising a halogenated xanthene.

10 (Twice Amended). A radiosensitizer agent for treatment of cancer and tumors using ionizing radiation, said radiosensitizer agent comprising a halogenated xanthene wherein said halogenated xanthene is activated using x-rays having an energy greater than 30 keV.

12 (Twice Amended). A radiosensitizer agent for treatment of cancer and tumors using applied ionizing radiation, said radiosensitizer agent comprising a halogenated xanthene, wherein said radiosensitizer agent substantially concentrates in said cancer or tumors.

16 (Twice Amended). The radiosensitizer agent of Claim 14 wherein said targeting is by partitioning of the radiosensitizer agent at a position proximate to or into the biologically sensitive structures of said cancer or tumors.

23 (Twice Amended). The radiosensitizer agent of Claim 15 wherein said targeting is by partitioning of the radiosensitizer agent at a position proximate to or into the biologically sensitive structures of said cancer or tumors.

25 (Twice Amended). The radiosensitizer agent of Claim 12 wherein said radiosensitizer agent is delivered by encapsulation of said radiosensitizer agent in a delivery vehicle.

51 (Twice Amended). A radiosensitizer agent for treatment of cancer and tumors using radiosensitization or ionizing radiation, said radiosensitizer agent comprising a halogenated xanthene wherein said ionizing radiation is approximately greater than or equal to 1 keV and less than or equal to approximately 1000 MeV.

54 (Amended). The radiosensitizer agent of Claim 12 wherein said halogenated xanthene is a functional derivative formed by attachment of at least one targeting moiety to said halogenated xanthene.

REMARKS

In the Final Rejection, the Examiner continued the following rejections:

(1) Claims 1-3, 5-8, and 12-13, plus new Claims 58-59 under 35 USC §102 as being anticipated by Serafini et al. (¶8);

(2) Claims 1-3, 5-9, and 12-13, plus new Claims 58-59 under 35 USC §102 as being anticipated by Neckers (¶10); and

(3) Claims 4, 14, 18-20, and 25-27 under 35 USC §103 as being unpatentable over Serafini et al. or Neckers in view of Khaw (¶15).

The Examiner also made the following new rejections:

(4) Claims 15-16, 23, and 54-55 under 35 USC §103 as being unpatentable over Serafini et al. or Neckers in view of Khaw (¶15); and

(5) Claims 10, 51, 52, and 56-57 under 35 USC §103 as being unpatentable over Serafini et al. or Neckers in view of Norman (1991) (¶16).

Each of these rejections is respectfully traversed, as explained below.

I. The §102 Rejections

A. First §102 Rejection

The Examiner rejects Claims 1-3, 5-8, 12-13, and 58-59 under 35 USC §102 as being "inherently anticipated by Serafini et al...for reasons of record." This rejection is respectfully traversed as the claimed invention and Serafini et al. are very different. Applicants believe that with a further explanation, these differences will become clear to the Examiner. Applicants acknowledge the withdrawal of the §102 rejection of claims 10, 15-16, 23, and 51 based on Serafini et al. Final Rejection, page 5, ¶9.

The present invention, as recited in independent Claims 1 and 12 and claims dependent thereon, is directed to a *radiosensitizer* agent for *treatment* of cancer and tumors using *ionizing radiation*, said radiosensitizer agent comprising a halogenated xanthene (Claims 1 and 12). Claim 12 also specifies that the radiosensitizer agent substantially concentrates in said cancer or tumors. As one skilled in the art would understand, such ionizing radiation for a radiosensitizer is applied ionizing radiation. In order to remove any possible misunderstanding, Applicants have added the term "applied" before "ionizing radiation" in independent Claims 1 and 12.[01]

In contrast, Serafini et al. does not disclose or suggest a halogenated xanthene radiosensitizer agent, a halogenated xanthene radiosensitizer agent for treatment or using (applied) ionizing radiation. Instead, Serafini et al. describes the use of certain radioactive forms of Rose Bengal in the medical evaluation of liver function. In a *diagnostic* test, a radioactive form of the compound (radiolabelled with iodine-131 or, as taught by Serafini et al., with iodine-123) is administered to the patient as an intravenous bolus. The subsequent distribution of the diagnostic agent throughout

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[01] Applicants do not believe that this amendment is a Festo type narrowing amendment but instead clarifies what one skilled in the art would understand, i.e. that ionizing radiation as recited in the claim is applied ionizing radiation.

certain organs of the patient's body is then determined by detecting the emissions resulting from the radioactive decay of the radioactive iodine contained in this radiolabelled Rose Bengal. Serafini et al. describes use of a radiation detection system for detecting the spontaneous radioactive decay of the radioactive iodine using a "scintillation camera" that is placed outside the patient's body. (The scintillation camera receives and produces an electrical or other signal based thereon). Serafini et al. is thus concerned with an application in nuclear medicine where the natural radioactivity of a substance is put to use. The substance in Serafini et al.'s case, Iodine-123-labeled-Rose Bengal, *emits* radiation which Serafini et al. report on for imaging purposes. As seems appropriate, this article appears in a journal directed to nuclear medicine. Fundamentally, this reference indicates the advantage of one radioactive form of rose bengal over another, in forming images from the radioactive emissions.

In the Final Rejection, the Examiner states (¶17a) that Serafini et al. teaches Rose Bengal:

> "which has an inherent capacity to rapidly and efficiently concentrate into cellular molecules upon exposure to ionizing radiation; thus, a radiosensitizer or a pharmaceutical agent which in combination with ionizing radiation, finds use in treating diseased tissue with overall reduction in radiation exposure to treat diseases such as cancer or tumor. Specifically, Applicant claims a radiosensitizer agent, halogenated xanthene, a known product clearly taught by Serafini et al. and which has the inherent property to concentrate into diseased tissue (as shown by Serafini et al.). Therefore, the product of the present invention is concluded to be inherently anticipated by Serafini et al."

Applicants respectfully but strongly disagree with the Examiner's conclusion and note that the Examiner has made no specific citation to any disclosure in Serafini et al. where "exposure to ionizing radiation" is shown. Nor has the Examiner shown a disclosure in this reference of using any halogenated xanthene to "treat diseases". Indeed, the Examiner has not pointed out where halogenated xanthenes are identified as "a radiosensitizer agent." In fact, Serafini et al. does not

disclose or suggest a radiosensitizer agent since no exogenous radiation is therapeutically, diagnostically or otherwise applied to the tissue containing the Rose Bengal. The fact that Serafini et al. teaches that Rose Bengal could be tagged with radioactive Iodine -123 (page 630, col. 1) does not mean that Rose Bengal is a radiosensitizer. And the teaching that Iodine -123 can be a useful substitute for ^{131}I as a label for radiopharmaceuticals likewise is not a disclosure that Rose Bengal is effective as a radiosensitizer. Additionally, Applicants find no suggestion of any therapeutic modality in Serafini et al. Further, any radiation emanating from I-123 or I-131 that hits the tissue as a result of the radioactive decay of the imaging agent would not be regarded as applied "ionizing radiation" by those skilled in the art. It clearly is not applied ionizing radiation.

Further, a central theme of Serafini et al. is the use I-123 instead of I-131 so as to minimize the effects of [emitted] radiation to tissues containing diagnostic quantities of radiolabeled Rose Bengal (as well as to minimize or avoid damage to surrounding tissues and to tissues containing degradation products of such radiolabeled Rose Bengal). For example, in the abstract, Serafini et al. states:

> "The overall reduction in imaging time and radiation exposure...should greatly improve our diagnostic capabilities in evaluating the jaundiced patient."

In the second paragraph (p. 629), Serafini et al. states:

> "Because of the relatively high absorbed radiation dose produced by the beta decay and the 8-day half life of [radiolabeled] ^{131}I rose bengal, we are limited in the amount of activity [of radiolabeled rose bengal] that can be administered to the patient..."

Finally, in the discussion (p. 631-632), Serafini et al. states:

> "Iodine-123 when compared with ^{131}I has several desirable physical properties.... The relatively short 13- hr half-life of ^{123}I decreases patient exposure [to radiation]..."

Thus, one of the fundamental concepts Serafini et al. is directed to is minimizing the effects of radiation in tissues containing Rose Bengal. This is completely the opposite of what is taught in the present invention, which seeks to maximize the effects of ionizing radiation in tissues containing Rose Bengal.

Also, Serafini et al. fails to teach that Rose Bengal targets diseased tissue (such as that of cancerous tumors), but instead illustrates that retention of Rose Bengal in portions of the liver and gall bladder can be used to diagnose function of these particular organs. Specifically, anomalous patterns of retention of Rose Bengal, as illustrated by Figs. 1 and 2 of Serafini et al., can be used to identify and diagnose areas of abnormal excretion of Rose Bengal. In normal organs, Rose Bengal is expected to exhibit a characteristic concentration half-life and should exhibit substantially uniform distribution (i.e., isotropic distribution) throughout the organ. Upon intravenous administration, a bolus of Rose Bengal perfuses a given organ, then gradually washes out as the bolus is cleared from the blood stream (or in the case of the liver or gall bladder, the Rose Bengal is excreted through normal physiologic functions of the organ, for example into the bile). In a diseased liver or gall bladder, anisotropic retention in certain portions of the organ is characteristic of reduced excretory function of such portions. Accordingly, the Rose Bengal in Serafini et al. is not targeting these diseased portions, but instead is merely backing up in these portions (i.e., it is not being excreted through such portions at a normal rate). It is further noted that because it is based on backing up in an organ, instead of targeting an organ, only the liver and gall bladder are discussed in Serafini et al. In short, this reference uses the radioactive quality of Iodine-123-Rose Bengal for diagnostic imaging -- just as its title states.

Therefore, for at least the above-stated reasons, there is no disclosure or suggestion in Serafini et al. of Rose Bengal or any other halogenated xanthene[02] as a radiosensitizer agent or as a radiosensitizer agent for treatment or using (applied) ionizing radiation with said radiosensitizer agent. Serafini et al. use of Rose Bengal is very different than the radiosensitizer agent of independent Claims 1 and 12 and in fact, appears to have almost no relevance to the present invention.

For the above-stated reasons, Applicants respectfully submit that the claims of the present application are not anticipated nor obvious over Serafini et al.

B. Second §102 Rejection

Applicants acknowledge the withdrawal of the §102(b) rejection of claims 10, 15-16, 25, and 51 over Neckers. The Examiner continues the rejection of Claims 1-3, 5-9, 12-13 and 58-59 under 35 USC §102 as being "inherently anticipated by Neckers." Final Rejection, ¶10-11. This rejection is also respectfully traversed, as Neckers is clearly different than the claimed invention.

The Examiner states that Neckers teaches Rose Bengal:

> "which has an inherent capacity to rapidly and efficiently concentrate into cellular molecules upon exposure to ionizing radiation; thus, a radiosensitizer or a pharmaceutical agent which in combination with ionizing radiation, finds use in treating diseased tissue. Specifically, Applicant claims a radiosensitizer agent, halogenated xanthene, a known product clearly taught by Neckers and which has the inherent property to concentrate into diseased tissue. Therefore, the product of the present invention is concluded to be inherently anticipated by Neckers."

Final Rejection, ¶17(b), pp. 9-10. Applicants respectfully traverse the Examiner's conclusion, along with many of the fact assertions about this reference.

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[02] Serafini et al. only mentions Rose Bengal and does not disclose the use of any other halogenated xanthene.

Neckers, according to its own summary, reports and compares the spectral properties, photochemical reactivity, and photophysical parameters of all known derivatives of Rose Bengal. As such, it describes the many fundamental chemical and physical properties of the halogenated xanthenes, particularly Rose Bengal. Neckers mentions a use "as a diagnostic probe," apparently in reference to Eosin. Neckers at 3. Among other things, Neckers further mentions a "fluorescence spectrum" of a certain salt, noting that it has "a broad triad of peaks centered at 583nm (Table 3)." Id. at 13. Neckers also mentions absorption and emission spectra, intermolecular energy transfer as measured by singlet oxygen yields, and intramolecular self-quenching. Id. at 18-21. A further discussion of quenching appears at pages 22-24.

The Examiner's assertion that Neckers discloses Rose Bengal as a radiosensitizer for use with ionizing radiation is not understood. The word "radiosensitizer" is used in the specification of the instant application, in a discussion of using ionizing radiation as a treatment for cancerous tumors, for example. The specification refers to a "radiosensitizer" in at least the following context,

> "The desired result is for radiation to become more efficacious when the radiosensitizer is present in tissue, so that less radiation is needed to treat the lesion tumor or other diseased tissue, and, accordingly, potential damage to surrounding healthy tissue, resulting from collateral exposure to the radiation, is reduced."

Specification, page 2, lines 17-20. An on-line dictionary defines "radiosensitizer" as follows:

> "A radiosensitizer is a substance given to a patient to make the intended target (such as a tumor) more susceptible to the effects of radiotherapy."

BioTech Life Science Dictionary (Attached hereto).

The Examiner's application of Neckers to support a section 102 rejection is not based on a fair reading of the Neckers disclosure, we submit. For example, Applicants see no statement in Neckers that Rose Bengal or another halogenated xanthene would be useful as a radiosensitizer for

ionizing radiation. The Examiner is respectfully requested to point out particularly the exact support from this reference for the proposition that these substances are radiosensitizers.

Applicants find no teaching or suggestion in Neckers of a halogenated xanthene as a radiosensitizer agent.

In addition, Applicants find no disclosure in Neckers of combining Rose Bengal or another halogenated xanthene with ionizing radiation.

Further, Applicants find no disclosure in Neckers of using such agents along with ionizing radiation for treatment of cancer or tumors, as required in the claims of the present application.

The Examiner makes reference to Rose Bengal concentrating into cellular molecules upon exposure to ionizing radiation. To the extent that the Examiner relies on Neckers for this teaching, Applicants do not see that disclosure in the reference and respectfully ask the Examiner to identify its location so Applicants can consider it more fully.[03] So far as Applicants are aware, Neckers describes only the interaction of optical radiation (i.e., ultraviolet, visible and near infrared light), not ionizing radiation with such agents.

In short, Applicants see nothing whatsoever in Neckers to indicate any application of any halogenated xanthene as a radiosensitizer. Merely identifying Rose Bengal or other halogenated xanthenes as known compounds or salts is far short of identifying them as radiosensitizers in the manner claimed.

Applicants also note that Neckers is published in *J. Photochem. Photobiol.*, a journal that has a topical focus on the interaction of optical radiation (i.e., ultraviolet, visible and near infrared light)

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[03] The Neckers that Applicants understand the Examiner to be citing is D.C. Neckers, "Rose Bengal", Journal of Photochemistry and Photobiology, A. Chemistry, 47 (1989) p. 1-29. If this is incorrect, the Examiner is respectfully requested to advise the undersigned immediately of the correct citation. If it is correct, the undersigned requests that the Examiner point to where in the reference this teaching is shown.

with matter, rather than on the interaction of x-rays, gamma-rays, and other high energy ionizing radiation with such matter. Such a journal is appropriate for the subject matter of Neckers, and is further indicative that Neckers concerns the interaction of *optical* radiation, not *ionizing* radiation, with Rose Bengal.

Accordingly, for the above-stated reasons, Neckers does not disclose or suggest the radiosensitizer agent of the claims of the present application, and the rejected claims are clearly not anticipated by Neckers but are patentable thereover. Applicants therefore respectfully traverse the rejection of these claims over Neckers as an anticipating reference and request that such rejection be withdrawn.

II. §103 Rejections

A. First §103 Rejection

The Examiner also rejects Claims 4, 14, 18-20 and 25-27 under 35 USC §103 as being unpatentable over Serafini et al. or Neckers in view of Khaw et al. Final Rejection, p. 6, ¶15 (first para.). This rejection is respectfully traversed.

As explained above, neither Serafini et al. nor Neckers discloses nor suggests any radiosensitizer, and certainly do not disclose nor suggest the radiosensitizer as claimed in the present application. As a result, even if these two references were combined[04], the combination still fails to disclose or suggest a halogenated xanthene radiosensitizer agent, a halogenated xanthene radiosensitizer agent for treatment, or the use of ionizing radiation with such a radiosensitizer agent, as claimed in the present application. Adding Khaw et al. to the combination does not cure the shortcomings, for Khaw et al., as will be explained below, fails to disclose the features of claim 1.

[04] Applicants do not admit that such a combination is proper.

As a result, the features of independent claim 1 are patentably distinct over the hypothetical combination, wherefore all claims dependent thereon are patentably distinct also.

Rejected dependent claims 4 and 14 concern targeting while rejected claims 18-20 and 25-27 concern other dependent features, encapsulation being one. This presumably is the reason for the citation of Khaw et al. Khaw et al. fails to disclose any of these claimed features of the present application. Instead, Khaw et al. discloses methods of manufacture and use of immunoliposomes (i.e., liposomes doped on their outside surface with an immunoactive moiety, such as an antibody). Such immunoliposomes are purported to provide means for targeted delivery of their contents to various immunologic targets (such as certain cancer cells) (*see, e.g.* col. 6, lns. 44-50). Use of such immunoliposomal delivery means is taught for use with therapeutic radioactive iodine (see col. 11, lns. 37-46) and for various "radiopaque" materials (*see* col. 11, lns 53-64). Specific examples of such use with contrast agents is given in Table I: Additional uses with radiosensitizing compounds is disclosed at col. 13, lns. 62-65. This is further discussed at col. 16, lns. 9-34 and lns. 52-60, and at col. 17, lns 13-16.

Notably, Khaw et al. teaches that such delivery is based primarily on action of a specific affinity reagent (i.e., the immunoactive moiety) with specific intracellular antigens, as taught at col. 3, lns. 14-21. This fundamental concept is markedly different than the teachings of the present invention, which discloses new radiosensitizer agents (i.e. halogenated xanthenes) that exhibit intrinsic targeting for certain types of cells and tissues along with certain structural components of such cells and tissues (see, e.g. p. 6, ln. 12 - p. 7, ln. 23, of the present application). As a result, Khaw et al. teaches away from the subject matter of the present invention by requiring use of specific immunologic delivery means and liposomal packaging for successful transport and delivery of radiocontrast or radiosensitizer agents to diseased tissue. In contrast, in the present invention, such

complex adjuvants are not required, but instead simple adjuvants (i.e. simple liposomal formulations, rather than Khaw et al.'s more complex immunoliposomes) can be used in the formulation and optimization of such agents for certain physical targeting purposes (see e.g. p. 7, lns. 17-21 of the present application). Thus, while Khaw et al. ***requires*** immunoliposomes for successful targeting and delivery of the liposomal contents, the present application does not have such a requirement.

Further, Khaw does not disclose or suggest the use of halogenated xanthenes as radiosensitizer agents.

Where none of the references in the hypothetical combination teach radiosensitizers for use with ionizing radiation, combining them fails to produce the missing teachings. Even when combined, these three references fail to disclose or suggest the radiosensitizer agent comprising a halogenated xanthene of the claims of the present application. Therefore, the claims are patentable over these references.

B. Second §103 Rejection

Claims 15-16, 23 and 54-55 under 35 USC §103 stand rejected as being unpatentable over Serafini et al. or Neckers in view of Khaw et al. Final Rejection, p. 7, ¶15 (second para.).

These dependent claims concern other dependent features, one concerning targeting moieties. For substantially the same reasons discussed above, the claims of the present application are patentable over these references for at least the reason that the parent claims are patentable over the hypothetical combination.

C. **Third §103 Rejection**

The Examiner also rejects Claims 10, 51, 52 and 56-57 under 35 USC §103 as being unpatentable over Serafini et al. or Neckers in view of Norman (1991)[05]. Final Rejection, p. 7, ¶16. This (new) ground of rejection is also traversed.

As explained above, neither Serafini et al. nor Neckers discloses or suggests the radiosensitizer according to the claims of the present application. As a result, even if these two were combined[06], the combination still fails to disclose or suggest a halogenated xanthene radiosensitizer agent, a halogenated xanthene radiosensitizer agent for treatment or the use of applied ionizing radiation with such a radiosensitizer agent, as claimed in the present application.

Norman also fails to disclose these limitations of the present invention. In fact, Norman actually teaches away from the claimed radiosensitizer agent of the present application in his teaching of three possible ways to increase the efficacy of radiosensitization: (1) irradiation at specific energies that are maximally absorbed by the radiosensitizer; (2) use of a novel agent with higher radiodensity, i.e. gadolinium; or (3) use of radiosensitizer agents that are directly incorporated into tumor cells (see "Discussion" on page S120 of Norman). In each of these elements, Norman teaches away from the subject matter of the claims of the present application.

In Norman's first example, he states that practitioners can use a specific activation energy of 32 KEV but that such energy will have a poor penetration through the skull and brain to a tumor. Hence, Norman admits that this method is undesirable. Further, there is no teaching in this method

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[05] Applicants herein propose to amend the form of Claim 10 but not its substance. The amendment makes Claim 10 independent, including its base claim and the limitations previously made in that claim. These amendments were made to correct informalities in the claims and are not narrowing Festo type amendments.

[06] Applicants do not admit that such a combination is proper.

of using a halogenated xanthene, as in the claims of the present invention In contrast to Norman, the present application teaches that the new halogenated xanthene class of radiosensitizer agents are compatible with a broad range of activation energies (see, for example, p. 9, line 20 - p. 10, line18). Thus, use of the halogenated xanthenes does not suffer from these serious limitations on activation energy as taught by Norman.

In Norman's second example, he requires that practitioners use an exotic radiodense material, gadolinium. In contrast, the claims of the present application require the use of a halogenated xanthene which overcomes the shortcomings of earlier classes of radiosensitizers. Gadolinium is not a halogenated xanthene.

In Norman's third example, he teaches the use of complex radiosensitizer/nucleic acid conjugates for enhanced agent incorporation into target cells. However, Norman specifically states that such means are "a difficult and expensive method as compared to injecting [more radiosensitizer]." (p. S121) Thus, Norman teaches away from one of the benefits of the subject matter of the present application by recommending that practitioners *use more agent*, rather than *a better agent*. Further, Norman notes that a clear obstacle to proceeding with his method is toxicity to the patient! Hence, Norman appears to be admitting that this teaching is infirm.

In contrast, the halogenated xanthene radiosensitizer agents of the claims of the present application exhibit intrinsic targeting and incorporation into tumor and other diseased tissue (see, for example, p. 6, line 13 - p. 7, line 23). Such intrinsic targeting does not require additional difficult or expensive methods for manufacture or use. Hence, these agents are far superior than those contemplated by Norman. Further, since the halogenated xanthene class of agent has a significant regulatory history and low agent cost (see p. 8, lines 2-4, of the present application), use of such agents does not represent an expensive method for radiosensitization, as purported by Norman.

Furthermore, numerous toxicology studies have shown that this class of agents (i.e. halogenated xanthenes) is non-toxic.

Thus, based on these substantive contradictions between the teachings of Norman and the claims of the present application, it is respectfully submitted that Norman would fail to motivate one of ordinary skill in the art to utilize halogenated xanthenes as radiosensitizers. Hence, such a combination is improper as one skilled in the art would not combine Norman with either Serafini et al. or Neckers, and none of the references suggest such a combination, as required by the Federal Circuit.

It is difficult to understand how the Examiner can combine references that nowhere disclose or suggest important features of the invention and emerge with the invention itself from the combination. Norman begins his discussion with the statement that iodinated contrast media (CM) enhance the radiation dose absorbed from diagnostic x-rays. Page S120, first sentence. He then mentions treating brain tumors. Id., second sentence. Norman says nothing about halogenated xanthenes in particular. Serafini et al. is concerned with scintillation photographs of a radioactive form of Rose Bengal (an halogenated xanthene), but says nothing about using halogenated xanthenes as a radiosensitizer. Neckers discusses Rose Bengal but again fails to suggest utility as a radiosensitizer. Since Serafini et al., Neckers, and Norman all fail to suggest halogenated xanthenes as a radiosensitizer for treating cancer and tumors using ionizing radiation, there can be no teaching from which these three references can be combined to arrive at the present invention. Further, Applicants submit that, even if arguably these references could be combined, when combined none of them discloses or suggests this feature of the claimed invention. Hence, even when combined, they fail to disclose the claimed invention, and the invention would not have been obvious in view of such a combination.

Moreover, since the 1991 date indicated for Norman, seven years passed before the filing of the parent application in 1998, with no publication nor public use (so far as Applicants are aware) of using Rose Bengal or any other halogenated xanthene as a radiosensitizer for treating tumors or cancer tissue with ionizing radiation. Given that cancer research is of global importance and focus, the passage of these several years following the publication of Norman, with no one appreciating the invention now claimed, is strong evidence of the non-obviousness of the claimed subject matter.

Accordingly, it is respectfully requested that this rejection be withdrawn.

III. §112 Rejection

In the Final Rejection, the Examiner rejects Claims 15-16, 23, 25-27 and 54 under 35 USC §112 as being indefinite. Applicants have amended claim 23 to recite "the biologically sensitive structures of said cancer or tumors" to correct a minor informality in the claim. Applicants have also make minor amendments to Claim 54 to remove any informalities in these claims.

Applicants believe that the remaining objected to claims are acceptable as written and wish to discuss this issue with the Examiner at the interview.

IV. Specification

Applicants are amending the specification to reflect the earlier application to which Applicants wish to claim priority. It is believed that no new matter is being added. Accordingly, it is requested that this amendment be entered and allowed.

Conclusion

For the above-stated reasons, it is respectfully submitted that the claims of the present application are neither disclosed nor suggested by the cited references and are patentable thereover. Accordingly, it is requested that the claims be passed to allowance.

Favorable reconsideration is earnestly solicited.

Respectfully submitted,

Date: April ___, 2001

_____
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Marked up copies of claims amended herein:

1 (Twice Amended). A radiosensitizer agent for treatment of cancer and tumors using [radiosensitization or] applied ionizing radiation, said radiosensitizer agent comprising a halogenated xanthene.

10 (Twice Amended). A radiosensitizer agent for treatment of cancer and tumors using ionizing radiation, said radiosensitizer agent comprising a halogenated xanthene [The radiosensitizer agent of Claim 1] wherein said halogenated xanthene is activated using x-rays having an energy greater than 30 keV.

12 (Twice Amended). A radiosensitizer agent for treatment of cancer and tumors using [radiosensitization or] applied ionizing radiation, said radiosensitizer agent comprising a halogenated xanthene, wherein said radiosensitizer agent substantially concentrates in said cancer or tumors.

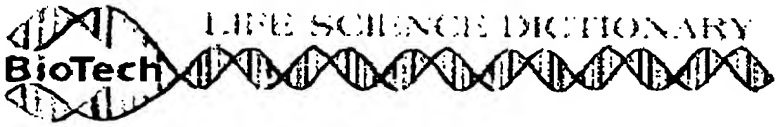
16 (Twice Amended). The radiosensitizer agent of Claim 14 wherein said targeting is by partitioning of the radiosensitizer agent at a position proximate to or into the biologically sensitive structures of said cancer or tumors.

23 (Twice Amended). The radiosensitizer agent of Claim 15 wherein said targeting is by partitioning of the radiosensitizer agent at a position proximate to or into the biologically sensitive structures of said cancer or tumors.

25 (Twice Amended). The radiosensitizer agent of Claim [15] 12 wherein said radiosensitizer agent is delivered by encapsulation of said radiosensitizer agent in a delivery vehicle.

51 (Twice Amended). A radiosensitizer agent for treatment of cancer and tumors using radiosensitization or ionizing radiation, said radiosensitizer agent comprising a halogenated xanthene [The radiosensitizer agent of Claim 1] wherein said ionizing radiation is approximately greater than or equal to 1 keV and less than or equal to approximately 1000 MeV.

54 (Amended). The radiosensitizer agent of Claim 12 wherein said halogenated xanthene is a functional derivative formed by attachment of at least one targeting moiety [at positions R^1 or R^2] to said halogenated xanthene.



Search Results

Search Terms: AND Search Definitions:

Contains this Begins with this Find Words! Clear Form

Total searching time: 0.00sec

Searching Category	User input query
DEFINITION search string	radiosensitizer
Number of Results	1

1. **radiosensitizer**
   Author: Guo Li
   Definition:
   A radiosensitizer is a substance given to a patient to make the intended target (such as a tumor) more susceptible to the effects of radiotherapy.

END